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Impact of primary and intravascular catheter-related bacteremia due to coagulase-negative staphylococci in critically ill patients

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KEYWORDS
Primary bacteremia;
Catheter-related bacteremia;
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Mortality;
Morbidity

Abstract
Objective: To study the impact of coagulase-negative staphylococcal (CNS) primary and intravascular catheter-related bloodstream infection (PBSI/CRBSI) on mortality and morbidity in critically-ill patients.
Design: We performed a double analysis using data from the ENVIN-HELICS registry data (years 1997 to 2008): 1) We studied the clinical characteristics and outcomes of patients with CNS-induced PBSI/CRBSI and compared them with those of patients with PBSI/CRBSI caused by other pathogens; and 2) We analyzed the impact of CNS-induced PBSI/CRBSI using a case-control design (1:4) in patients without other nosocomial infections.
Setting: 167 Spanish Intensive Care Units.
Patients: Patients admitted to ICU for more than 24 hours.
Results: 2,252 patients developed PBSI/CRBSI, of which 1,133 were caused by CNS. The associated mortality for PBSI/CRBSI caused by non-CNS pathogens was higher than that of the CNS group (29.8% vs. 25.9%; P = .039) due exclusively to the mortality of patients with candidemia (mortality: 45.9%). In patients without other infections, PBSI/CRBSI caused by CNS (414 patients) is an independent risk factor for a higher than average length of ICU stay (OR: 5.81, 95%CI: 4.31-7.82; P < .001).

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Conclusion: Crude mortality of patients with CNS-induced BPSI/CRBSI is similar to that of patients with BPSI/CRBSI caused by other bacteria, but lower than that of patients with candidemia. Compared to patients without nosocomial infections, CNS-induced PBSI/CRBSI is associated with a significant increase in length of ICU stay
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PALABRAS CLAVE
Bacteriemia primaria;
Bacteriemia relacionada con catéter;
Staphylococcus coagulas negativo;
Mortalidad;
Morbilidad

Impacto de la bacteriemia primaria y relacionada con catéter intravascular causada por *Staphylococcus* coagulasa negativo en pacientes críticos

Resumen
Objetivo: Estudiar el impacto en la mortalidad y morbilidad en pacientes críticos de las bacteriemias primarias (BP) y relacionadas con catéteres intravasculares (BRC) causadas por *Staphylococcus* coagulasa negativo (SCN).
Diseño: Doble análisis con datos del registro ENVIN-HELICS (1997 a 2008): 1) analizar las características clínicas de pacientes con BP/BRC causadas por SCN, comparándolas con las de los pacientes con BP/BRC causadas por otros patógenos; y 2) analizar mediante un estudio casos-controles (1:4) el impacto de BP/BRC por SCN en pacientes sin otras infecciones nosocomiales frente a pacientes sin ninguna infección nosocomial.
Ámbito: Ciento sesenta y siete UCI españolas.
Pacientes: Pacientes ingresados en UCI más de 24 horas.
Intervención: Ninguna.
Variables de interés: Estancia en UCI y mortalidad.
Resultados: Dos mil doscientos cincuenta y dos pacientes presentaron BP/BRC de los que 1.133 casos fueron por SCN. La mortalidad de los pacientes con BP/BRC causadas por patógenos distintos de SCN fue superior (29,8%vs. 25,9%; p = 0,039), debido exclusivamente a la mortalidad de pacientes con candidemia (mortalidad: 45,9%). En pacientes sin otras infecciones nosocomiales, la BP/BRC por SCN (414 pacientes) es un factor independiente de riesgo de tener una estancia superior a la media (OR 5,81; IC 95% 4,31-7,82; p < 0,001).
Conclusión: La mortalidad cruda de los pacientes que padecieron BP/BRC causada por SCN es similar a la de los pacientes con BP/BRC causada por otras bacterias, pero inferior a la de los pacientes con candidemia. Comparándolo con la estancia en UCI de pacientes sin infecciones nosocomiales, la BP/BRC por SCN es un factor apreciable de prolongación de estancia.
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Introduction

Bacteremia caused by coagulase-negative *Staphylococcus* (CNS) represents one of the most common nosocomial infections in patients admitted to the Intensive Care Unit (ICU). This family of pathogens includes very frequent species of microorganisms such as *S. epidermidis* (accounting for over 50% of all infections caused by CNS), together with less common species such as S. *haemolyticus*, *S. hominis, S. lugdunensis, S. schleiferi* and *S. saprophyticus*, among others.[1] Some of these species produce specific infections such as urinary infections caused by S. saprophyticus, or infections of considerable seriousness such as endocarditis or osteomyelitis caused by *S. lugdunensis* or *S. schleiferi*.

In general, infections caused by CNS are not regarded as particularly serious, and in many cases when such processes are secondary to central venous catheters no antibiotic treatment is required, and healing is achieved after removing the intravascular device or following a short course of antimicrobial treatment.[2]

Little is known of the true impact of primary bacteremias (PB) and of bacteremias secondary to central venous catheter placement (i.e., catheter-related bacteremia, CRB) caused by CNS. Univariate analyses of the data found in old publications[3] indicate excessive mortality and stay as a result of bacteremias caused by CNS, though in contrast general studies of the repercussions of bacteremia upon patient morbidity-mortality indicate that such situations caused by CNS exert no influence upon mortality.[4,5] No specific studies in critically ill patients have compared the repercussions of primary and intravascular catheter-related bacteremias (PB/CRB) caused by CNS versus the repercussions in patients with bacteremia caused by other pathogens, or without bacteremia.

An added difficulty is the fact that CNS colonizes the skin. As a result, the isolation of these pathogens in blood cultures may be due to contamination at the time of sample collection. The Microbiology laboratory must attempt to identify the strains suggesting contamination,[6-8] with the support of clinical and laboratory test data for confirmation.[9]

The present study examines the impact upon patient morbidity-mortality of primary bacteremias and central venous catheter-related bacteremias caused by CNS, establishing comparisons with patients presenting bacteremia caused by other microorganisms on one hand, and with patients presenting no nosocomial infection during admission to the ICU on the other.

Patients and methods

The present study contemplates dual methodology: 1) a study of the differential characteristics of patients with PB/CRB due to CNS and of patients with bacteremia caused by other microorganisms, based on a cohort survey involving a descriptive and multivariate analysis; and 2) a study of the impact of bacteremia due to CNS in patients without other nosocomial infections, versus patients without PB/CRB or other nosocomial infections, based on a case-control study. The principal study variables are stay in the ICU as an indicator of raw morbidity and mortality during admission to the ICU.

The data were obtained from the registry of the National Vigilance Study of Nosocomial Infection in the ICU (ENVIN-HELICS)[10] – a registry auspiced by the Infectious Diseases working Group of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (*Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias*, SEMICYUC). An analysis has been made of the data collected in periods of three annual months between 1997 and 2008, corresponding to patients admitted to the ICU for more than 24 hours.

The patients were monitored until discharge from the ICU, or for a maximum of 60 days. For all selected patients we collected demographic information (date of birth and sex), background disease, instrumentation received, hospital stay prior to admission to the ICU, stay in the ICU, and clinical situation at the time of discharge. In the case of some variables, related to the risk of developing nosocomial infection, data were only available from the year 2006, when the database was expanded.

The definitions are found in the registry manual, and customized software was used for data collection (access at: http://hws.vhebron.net/envin-helics/). Patient severity was evaluated using the APACHE II score,[11] and optionally the SAPS II,[12] upon admission to the ICU.

An analysis was made of PB, CRB and both conditions jointly (PB/CRB), as in other publications,[13,14] occurring from 48 hours after admission to the ICU. Based on the criteria of the Centers for Disease Control and Prevention (CDC),[15] primary bacteremia has been defined as the presence of a clinical condition compatible with infection and the obtainment of positive blood cultures in the absence of any known focus of infection. Catheter-related bacteremia in turn has been defined as isolation of the same microorganism in peripheral blood and the tip or connections of a central venous catheter, in all cases associated to a compatible clinical picture. When the isolated pathogen is a microorganism that colonizes the skin, such as CNS, two blood cultures positive for the same pathogen are required.

Patient selection

A total of 167 ICUs participated in the study (from 51 in the first year to 118 in the last year), with the recruitment of between 2393 patients in the year 1997 and 13,833 patients in 2008. In total, the present analysis included 85,246 patients, with 2935 episodes of PB/CRB (3165 isolated microorganisms) in 2412 patients. In those subjects with more than one PB/CRB episode, we selected the first episode. We excluded bacteremias involving more than one causal pathogen. In those cases where another microorganism of the skin was isolated in addition to a pathogen, we assigned the etiology of bacteremia to the non-skin colonizing pathogen. Based on these criteria, the initial case database comprised a total of 2252 patients.

Methodology

A first comparative analysis was made between patients with bacteremia due to CNS and patients with bacteremia caused by other pathogens, dividing the latter into cases caused by gramnegative bacilli (GB), other grampositive cocci (GPC) and Candida spp. Secondly, a case-control study (1:4) study was made, in which the cases corresponded to patients with a single bacteremia episode due to CNS and who during admission to the ICU presented no other nosocomial infection of those controlled in the ENVIN-HELICS (ventilator-associated pneumonia, catheter-related urinary infection and primary bacteremia and central venous catheter-related bacteremia). The controls in turn consisted of patients without any nosocomial infection of those cited above. This strict selection of patients allowed us to rule out the influence of other nosocomial infections upon mortality or stay.

The following pairing variables were used: sex, age (± 10 years), year of admission (between 1997 and 2008), background disease (coronary, medical, surgical or traumatologic), APACHE II score upon admission to the ICU (± 5 points)(or the SAPS II (± 10 points) in those cases where the APACHE II score was not available), and control subject duration of stay equal to or longer than the time of appearance of bacteremia among the cases – thus assuming longer stay among the cases from that moment onwards to be attributable to the bacteremia. Only those patients who survived were considered in the study of the impact upon stay.

Statistical analysis

A descriptive analysis was made in which the continuous variables were reported as the mean and 95% confidence interval (95%CI) for variables with a normal distribution, and as the median and interquartile range (IQR) in the case of variables with a non-normal or skewed distribution, such as stay. The qualitative variables in turn were expressed as frequency and percentage.

The chi-squared test was used for the comparison of percentages. Calculation of the statistical differences in quantitative variables between the groups of pathogens was based on the Kruskal-Wallis H test for independent samples, while comparison of the median stay in the ICU was made using the Mann-Whitney U-test. Logistic regression analysis in turn was carried out to identify the factors related to the appearance of bacteremia due to CNS, while conditional logistic regression was used to measure the impact of bacteremia upon the duration of stay – taking as cutoff point the mean days of stay of the cohort resulting from the pairing of cases and controls. The statistical analysis was carried out using the SPSS version 16.0.1 statistical package (SPSS® Inc., Chicago, IL, USA).

Results

The mean incidence of PB/CRB in all the participating ICUs was 6.61 bacteremias per 1000 central venous catheter days, and ranged between 7.93 (year 2004) and 4.65 (year 2007) episodes per 1000 central venous catheter days.

Table 1 describes the general characteristics of the 2252 patients presenting primary and catheter-related

Table 1 Description of the population with monomicrobial bacteremia

Factor[a]	n = 2252
Sex (male)	1557 (69.1%)
Age (m. 95%CI)	56.9 (56.2-57.6)
Background disease	
Coronary	165 (7.3%)
Medical	1241 (55.1%)
Surgical	465 (20.8%)
Traumatologic	381 (16.9%)
Emergency surgery	712 (31.6%)
Mechanical ventilation	2006 (89.1%)
Central venous catheter	2152 (95.6%)
Urinary catheter	2180 (96.8%)
Immunosuppression (916)	92 (10.1%)
Neutropenia (916)	29 (3.2%)
Immune deficiency (916)	34 (3.7%)
Antibiotic treatment (916)	828 (90.4%)
Parenteral nutrition (916)	376 (36.9%)
Ventricular shunt (916)	68 (7.4%)
Extrarenal filtration (916)	150 (16.4%)
Inflammatory response (902)	
Sepsis	616 (68.3%)
Severe sepsis	167 (18.5%)
Septic shock	119 (13.2%)
Number of nosocomial infections	
1	872 (38.7%)
2	668 (29.7%)
3	358 (15.9%)
4	164 (7.3%)
≥ 5	190 (8.4%)
APACHE II (m. 95%CI) (2103)	19.0 (18.8-19.3)
SAPS II (m. 95%CI) (654)	38.8 (37.3-40.2)
Type of bacteremia	
Primary	1033 (45.9%)
Catheter-related	1219 (54.1%)
Etiology of bacteremia	
Coagulase-negative *Staphylococcus*	1133 (50.3%)
Gramnegative bacilli	360 (16.0%)
Enterococcus spp.	180 (8.0%)
Pseudomonas spp.	132 (5.9%)
Methicillin-sensitive *Staphylococcus aureus*	131 (5.8%)
Candida spp.	109 (4.8%)
Acinetobacter spp.	95 (4.2%)
Methicillin-resistant *Staphylococcus aureus*	61 (2.7%)
Other grampositive cocci	51 (2.3%)
Stay in ICU prior to infection (mdn [IQR]; m)	11 [6-17]; 13.2
Stay in ICU after infection (mdn [IQR]; m)	12 [6-21]; 15.0
Total stay in ICU (mdn [IQR]; m)	25 [15-36]; 27.2
Mortality	626 (27.8%)

m: mean: mdn: median; [IQR] interquartile range (25-75%).

[a]The number of cases with data for each variable are shown in parentheses.

Table 2 Comparison of patients with bacteremia due to coagulase-negative Staphylococcus (CNS) and patients with bacteremia caused by other microorganisms

Factor	CNS n = 1133	GNB n = 587	Other GPC n = 423	Candida spp. n = 109	p
Sex (male)	801 (70.7%)	400 (68.1%)	288 (68.1%)	68 (62.4%)	0.250
Age (m. 95%CI)	56.1 (55.1-57.1)	57.6 (56.2-59.0)	57.2 (55.5-58.8)	60.2 (57.3-63.1)	0.060
Background disease					0.004
Coronary	69 (6.1%)	50 (8.5%)	44 (10.4%)	2 (1.8%)	
Medical	624 (55.1%)	320 (54.5%)	224 (53.0%)	73 (67%)	
Surgical	238 (21.0%)	125 (21.3%)	90 (21.3%)	12 (11%)	
Traumatologic	202 (17.8%)	92 (15.7%)	65 (15.4%)	22 (20.2%)	
Emergency surgery	374 (33%)	177 (30.2%)	120 (28.4%)	41 (37.6%)	0.369
Mechanical ventilation	1009 (89.1%)	532 (90.6%)	362 (85.6%)	103 (94.5%)	0.018
Central venous catheter	1056 (95.9%)	549 (96.5%)	381 (94.3%)	107 (98.2%)	0.212
Urinary catheter	1094 (96.6%)	570 (97.1%)	409 (96.7%)	107 (96.8%)	0.786
Immunosuppression[a]	45 (9.8%)	29 (11.1%)	13 (9.2%)	5 (8.9%)	0.908
Neutropenia[a]	15 (3.3%)	9 (3.4%)	4 (2.8%)	1 (1.8%)	0.921
Immune depression[a]	20 (4.4%)	11 (4.2%)	0	3 (5.4%)	0.084
Antimicrobial treatment[a]	416 (91.0%)	230 (88.1%)	129 (90.8%)	53 (90.3%)	0.398
Parenteral nutrition[a]	206 (45.1%)	89 (34.1%)	47 (33.1%)	34 (60.7%)	<0.001
Ventricular shunt[a]	38 (8.3%)	19 (7.3%)	10 (7.0%)	1 (1.8%)	0.368
Extrarenal filtration[a]	76 (16.6%)	38 (14.6%)	20 (14.1%)	16 (28.6%)	0.064
Inflammatory response[b] (902)					<0.001
Sepsis	347 (76.8%)	151 (58.5%)	93 (67.4%)	25 (46.3%)	
Severe sepsis	71 (15.7%)	54 (20.9%)	27 (19.6%)	15 (27.8%)	
Septic shock	34 (7.5%)	53 (20.6%)	18 (13.0%)	14 (25.9%)	
Number of nosocomial infections					<0.001
1	684 (60.4%)	315 (53.6%)	278 (65.7%)	59 (54.1%)	
2	345 (30.5%)	197 (33.6%)	97 (22.9%)	33 (30.3%)	
3	68 (6.0%)	45 (7.7%)	38 (9.0%)	9 (8.2%)	
4	23 (2.0%)	19 (3.2%)	8 (1.9%)	4 (3.7%)	
≥ 5	13 (1.1%)	11 (1.9%)	2 (0.5%)	4 (3.7%)	
APACHE II (m. 95%CI)[b](2103)	18.9 (18.4 –19.4)	19.5 (18.8-20.1)	18.3 (17.5-19.1)	20.1 (18.7-21.5)	0.077
SAPS II (m. 95%CI)[b] (654)	39.1 (37.1 –41.1)	39.6 (36.6-42.5)	35.9 (32.3-39.5)	41.4 (33.6-48.42)	0.354
Type of bacteremia					<0.001
Primary	439 (38.7%)	307 (52.3%)	236 (55.8%)	51 (46.8%)	
Catheter-related	694 (61.3%)	280 (47.7%)	187 (44.2%)	58 (53.2%)	
Stay in ICU prior to infection (mdn [IQR]; m)	10 [6 - 16]; 12.6	12 [7-20]; 14.2	10 [5-16]; 12.8	13; [9-19]; 15.2	0.532
Stay in ICU after infection (mdn [IQR]; m)[c]	13 [7 –22]; 15.9	10 [6-19]; 13.5	11; [5-20]; 13.8	14 [8-25.5]; 18.2	0.630
Total stay in ICU (mdn [IQR]; m)[c]	24 [16-36]; 27.5	25 [15-35]; 26.7	22 [13-34]; 25.6	29 [21-42.5]; 32.3	0.088
Mortality	293 (25.9%)	163 (27.8%)	120 (28.4%)	50 (45.9%)	<0.001

m: mean; mdn: median; [IQR] interquartile range (25%75%).
[a]Data available on 916 patients.
[b]The number of cases with data for each variable are shown in parentheses.
[c]Stay of patients calculated in the patients who survived.

Table 3 Multivariate analysis selecting coagulase-negative Staphylococcus as the etiology of bacteremia versus other pathogens

Factor	OR	95%CI	p
Due to catheter[a]	1.58	1.20-2.09	0.001
Parenteral nutrition	1.62	1.21-2.16	0.001
Bacteremia < 10 days in ICU	1.89	1.43-2.50	<0.001
Severe sepsis or septic shock	0.42	0.31-0. 56	<0.001

[a]With respect to patients with primary bacteremia.

bacteremia during admission to the ICU. In 1219 cases (54.1%) the diagnosis was catheter-related bacteremia, while the remaining 1033 cases (45.9%) were classified as primary bacteremia, since no infectious focus was identified. A total of 50.3% (1133 cases) of the bacteremias were caused by CNS.

Table 2 shows the characteristics of the patients with PB/CRB according to the etiology of the causal pathogen. There are global significant differences in the background disease and in the percentage of patients with parenteral nutrition, with an increased frequency in the CNS (45.1%) and Candida spp. groups (60.7%). Systemic inflammatory response, which was known in 902 patients, proved less severe in the patients with PB/CRB caused by CNS, since severe sepsis or septic shock was only recorded in 23.2% of the cases, while in the other groups the proportion exceeded 30%, reaching 53.7% in the Candida spp group. The percentage of CRB was higher in the episodes caused by CNS (61.3%), followed by Candida spp (53.2%).

The raw mortality of the patients with PB/CRB caused by pathogens other than CNS was greater than in those patients with PB/CRB due to CNS (29.8 vs. 25.9%; p = 0.039), though the difference was attributable to the influence of those patients who suffered PB/CRB caused by Candida. The raw mortality of the patients with PB/CRB due to CNS (25.9%) was similar that caused by gramnegative bacilli (GNB) (27.8%) and other grampositive cocci (GPC) (28.4%), but lower than the mortality associated to Candida spp. (45.9%). The latter was significantly differentiated with respect to PB/CRB due to CNS (OR: 0.56, 95%CI 0.39-0.80; p = 0.001), PB/CRB due to GNB (OR: 0.60, 95%CI 0.41-0.88; p = 0.008), and PB/CRB due to other GPC (OR: 0.61, 95%CI 0.49-0.91; p = 0.015).

In the multivariate analysis to identify the factors related to the appearance of bacteremia due to CNS, the independent factors were found to be a central venous catheter origin of bacteremia instead of primary bacteremia, the administration of parenteral nutrition, and a stay at the time of infection of under 10 days (Table 3). In contrast, the presence of severe sepsis or septic shock as systemic inflammatory response to bacteremia was seen to be related to bacteremia attributable to other pathogens (OR: 0.42, 95%CI 0.31-0.56; p < 0.001).

In the case-control study, selecting patients with a single episode of bacteremia due to CNS and without other nosocomial infections as cases, and patients without no nosocomial infection as controls, differences were observed (Table 4) in the percentage utilization of devices (mechanical ventilation, central venous catheter and urinary catheter), in the percentages of patients with emergency surgery during admission to the ICU, and in the use of antibiotic treatment, parenteral nutrition and extrarenal filtration. Considering only the patients that survived, the stay in the ICU was found to be longer in those with bacteremia due to CNS than in those without bacteremia (difference of medians 9 days; p < 0.001).

The mean duration of stay in the non-deceased case-control cohort (1582 patients) was 11.77 days. Analysis of the prolongation of stay in the paired cohort (Table 5) identified as independent factors of stay ≥ 12 days the presence of a urinary catheter, central venous catheter and mechanical ventilation, and bacteremia due to CNS likewise increased the risk of prolonged stay (OR: 5.81, 95%CI 4.31-7.82; p < 0.001).

Discussion

The main conclusions of this study are the following: 1) In highly selected cases, when the patient remains in serious condition requiring the maintenance of mechanical ventilation, with urinary and central venous catheterization, the development of primary bacteremia or catheter-related bacteremia due to CNS increases the risk of a longer stay in the ICU almost 6-fold versus the average duration of stay. 2) In patients with PB/CRB, episodes caused by CNS are more likely in patients with parenteral nutrition, when the catheter is the cause of the infection (in contrast to primary bacteremias), when bacteremia occurs after less than 10 days of stay in the ICU, and when the patient does not present a systemic inflammatory response in the form of severe sepsis or septic shock.

In this context, our data indirectly coincide with those reported in the literature.[4,5] In a recent metaanalysis, Siempos et al.[16] concluded that there is mortality attributable to catheter-related infection, but that the studies reporting the lowest mortality figures are those with a larger proportion of CNS.[17] In adult subjects, only the case-control study of Martin et al.[3] demonstrated an attributed mortality of 13% and a prolongation of hospital stay of 8.5 days. In other more recent studies,[4,14] no influence has been found on the part of PB/CRB caused by CNS in relation to mortality.

There is important variation in the proportion of CNS in the total nosocomial bacteremias studied. The European HELICS study reports a percentage of 17-44%, depending on the country.[18] This same report describes a figure of 34% for Spain, though in our study, on considering only monomicrobial bacteremia and the first bacteremia episode in each patient, the proportion was seen to reach 50%.

The main complexity of our study is its design. In effect, a first consideration is the fact that joint analysis was made of the primary bacteremias and catheter-related bacteremias. It has been reported that in those patients with a central venous catheter and bacteremia involving an unknown infectious focus, most cases are attributable to the catheter –though there are no studies offering an in-depth evaluation of this issue. Other studies[13,14,19] have also used this approach.

The first analysis aimed to offer information on the differences between PB/CRB caused by CNS and that caused

Table 4 Characteristics of the patients with bacteremia due to coagulase-negative Staphylococcus (CNS) versus the paired group without bacteremia or other nosocomial infections

Factor	CNS n = 414	Without bacteremia N = 1648	p
Sex (male)[a]	297 (71.7)	1187 (72.0%)	0.907
Age (m. 95%CI)[a]	55.9 (54.2-57.6)	56.8 (55.3-57.0)	0.764
Background disease[a]			0.999
Coronary	31 (7.5%)	124 (7.5%)	
Medical	228 (55.1%)	911 (55.3%)	
Surgical	84 (20.3%)	336 (20.4%)	
Traumatologic	71 (17.1%)	277 (16.8%)	
Year of admission[a]			0.329
1997	13 (3.1%)	54. (3.3%)	
1998	19 (4.6%)	70 (4.2%)	
1999	35 (8.5%)	138 (8.4%)	
2000	29 (7.0%)	122 (7.4%)	
2001	20 (4.8%)	81 (4.9%)	
2002	41 (9.9%)	155 (9.4%)	
2003	33 (8.0%)	133 (8.1%)	
2004	48 (11.6%)	192 (11.7%)	
2005	48 (11.6%)	189 (11.5%)	
2006	35 (8.5%)	145 (8.8%)	
2007	36 (8.7%)	143 (8.7%)	
2008	57 (13.8%)	226 (13.7%)	
APACHE II (m. 95%CI)(391/1497)[a]	17.9 (17.2-18.7)	17.6 (17.2-17.9)	0.466
SAPS II (m. 95%CI)(110/158)[a]	37.4 (33.9-40.8)	34.8 (32.4-37.1)	0.383
Emergency surgery	122 (29.5%)	342 (20.8%)	<0.001
Mechanical ventilation	322 (80.2%)	928 (56.3%)	<0.001
Central venous catheter	371 (92.8%)	1263 (79.5%)	<0.001
Urinary catheter	386 (93.2%)	1445 (87.7%)	0.001
Immunosuppression[b]	9 (7.0%)	36 (7.0%)	0.991
Neutropenia[b]	1 (0.8%)	11 (2.1%)	0.310
Immune deficiency[b]	3 (2.3%)	13 (2.5%)	0.904
Antibiotic treatment[b]	111 (86.7%)	331 (64.4%)	<0.001
Parenteral nutrition[b]	41 (32.0%)	43 (8.4%)	<0.001
Ventricular shunt[b]	5 (3.9%)	11 (2.1%)	0.255
Extrarenal filtration[b]	16 (12.5%)	14 (2.7%)	<0.001
Total stay in ICU[c] (mdn [IQR]; m)	17 [11-24]; 18.8	8 [5-13]; 9.9	<0.001
Mortality	82 (19.8%)	286 (17.4%)	0.244

[a]Pairing variables used.
[b]Data only from 128 patients with bacteremia due to CNS and 514 controls.
[c]Data referred to the patients that did not die in the ICU: 332 patients with bacteremia due to CNS and 1250 controls.

Table 5 Multivariate analysis of prolonged stay (≥ 12 days) in the paired cohort with primary bacteremia and catheter-related bacteremia due to coagulase-negative *Staphylococcus* (CNS), and patients without bacteremia

Factor	OR	95%CI	p
Urinary catheter	1.89	1.09-3.28	0.024
Central venous catheter	1.97	1.32-2.96	0.001
Mechanical ventilation	3.35	2.53-4.43	<0.001
Bacteremia due to CNS	5.81	4.31-7.82	<0.001

by other microorganisms, grouped from a microbiological perspective. The group of patients with PB/CRB in which the etiology was Candida spp. was clearly differentiated from the other groups, exhibiting increased mortality, and with differences versus any of the other patient bacteremia etiological groups. It must be taken into account that we considered raw mortality, and referred only to the first bacteremia episode in each patient –without adjusting for severity at the time of the bloodstream infection. Likewise, no evaluation was made of the influence of other nosocomial infections upon mortality. Our results suggest that there are no differences in the raw mortality of the patients with PB/CRB caused by CNS versus the episodes caused by other bacteria.

Globally considering PB/CRB due to other pathogens allows us to identify those patients more likely to have CNS as the causal agent and thus not start antibiotic treatment until patient response to withdrawal of the catheter has been evaluated.

Our study indicates that patients with BR/CRB caused by CNS have a lesser systemic inflammatory response than patients with the same bacteremias but caused by other microorganisms. Since mortality is related to such inflammatory response,[20] it seems reasonable to accept the absence of related mortality in patients with PB/CRB caused by CNS.

The careful patient selection in the second part of our study is justified by the fact that these patients present other factors related to mortality and the prolongation of stay. The presence of other nosocomial infections,[21] recorded in 60%of the patients studied, is one of the most important factors. For this reason we selected those patients without other nosocomial infections. Although such selection is "artificial", we used pairing of the cases and controls to take into account the risk of a similar duration of stay, not the fact of a greater risk or not of presenting PB/CRB. In our opinion, the development of PB/CRB due to CNS is not innocuous, since it favors a longer stay in the ICU in patients who inherently present a background disease process requiring admission to critical care.

This study has several limitations. A first consideration is the voluntary and multicenter nature of the ENVIN-HELICS project, where each center has its own policy regarding discharge from the Unit (due for example to the presence or absence of intermediate care levels). On the other hand, in central venous catheter-related infections, the approach to withdrawal of the catheter is a therapeutic action in itself, but the ENVIN-HELICS program provides no instructions on this point, since the adopted approaches may differ from those recommended in the clinical guides. Likewise, we do not know the antibiotic treatment used or not used in each case, though all patients had been treated by intensivists with adequate knowledge of the existing recommendations in this respect.

Furthermore, regarding the diagnosis, it is generally considered that the clinical picture must be compatible, and that two sets of positive blood cultures must be obtained in order to consider the episode as being clinically relevant. However, the software application has no controls in this respect, and so it is assumed that all the physicians reporting data know and follow the standard procedures. Lastly, in the case of some of the variables, only data from the year 2006 onwards have been collected –this being the year in which the database was modified to expand the number of variables registered. This has resulted in a restriction of the number of cases with these variables to 40%- a fact that can affect the statistical power on incorporating variables corresponding to the last years of the study, and may influence the results of the multivariate analysis of mortality.

In conclusion, the data of our study indicate that PB/CRB caused by CNS has no attributable influence upon mortality, though in certain circumstances, in critical adult patients such bacteremia is an important factor that can condition a longer stay in the ICU.

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Conflict of interest

The authors declare no conflict of interest.

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